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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/315,298 | 05/20/1999 | CHING-LEOU TENG | ISIS-3510 | 6350 |

34138 7590 08/26/2003

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

| EXAMINER |
|---|
| EPPS FORD, JANET L |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | 39 |

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/315,298 | TENG ET AL. | |
| | Examin r | Art Unit | |
| | Janet L. Epps-Ford, Ph.D. | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4-7,10,12,13,15,17,19,20,80,84,85 and 87-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,10,12,13,15,17,19,20,80,84,85 and 87-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *36* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Response to Arguments*

### *Claim Rejections - 35 USC § 102*

2. Claims 1, 5-7, 10, 17, and 19-20 remain rejected, and claims 87-96 are rejected under 35 U.S.C. 102(b) as being anticipated by Kawai et al. for the reasons of record set forth in the Official Action mailed 10-28-2002.

3. Applicant's arguments filed 2-27-03 have been fully considered, but they are not persuasive. Applicants traverse the instant rejection on the grounds that Kawai et al. does not teach a composition in a dosage form suitable for non-parental administration. Contrary to Applicant's assertions, Kawai et al. teach a composition comprising at least one antisense oligonucleotide in an emulsion and at least one fatty acid penetration enhancer, and further wherein said antisense oligonucleotide modulates expression of a cellular adhesion protein.

As stated in the prior Office Action, Kawai et al. disclose lipid microsphere in fat emulsion as a carrier to transducing gene DNA (i.e., microemulsion). These compositions comprise at least a transducing gene DNA, wherein said transducing gene DNA is synthetic oligonucleotide, such as the so-called phosphorothioate type, or it is a structural gene integrated into a vector (page 13, last paragraph of Japanese translation). Moreover, the compositions of the Kawai et al. invention comprise a transducing-gene DNA; fat emulsion base of at least one kind chosen from a vegetable oil, triglyceride of the medium chain triglyceride of 8-12 carbon atoms (such as capric, lauric and caprylic

acid, see page 16, paragraph [0013]), fatty acids of 6-18 carbon atoms (penetration enhancer); the emulsifier of at least one kind chosen from a phospholipid and a nonionic surface active agent; a cholesterol derivative; and water (see summary of the invention, page 3 of the Japanese translation). It is assumed from the reference that the emulsions are oil-in water emulsions since they are described in the Japenese translation as being fat emulsions wherein the water serves as the solvent (page 18, paragraph [0016] of translation).

The "transducing-gene DNA" of Kawai et al. is chosen from cancer suppression gene DNA, gene DNA of an interleukin-1, interleukin-2, interleukin-4, interleukin-6, interleukin-7, GM-CSF, TNF-alpha, interferon-c, PDGF (cell adhesion protein), HVS-tk, diptheria-toxin A, and cytosine deaminases (see 3rd paragraph of page 5, Japanese translation).

In another embodiment of Kawai et al., an emulsifier is distributed above the fat emulsion, wherein the emulsifier is a phospholipid or a nonionic surface active agent, wherein said agent is polyoxyethylene-(20)-ether (page 17, paragraph [0015]).

Moreover, the fat emulsions of Kawai et al. can be made to contain further additive agents, such as an isotonizing agent emulsification support agent, a stabilizer (for example, wherein said stabilizer is dextran see page 20, paragraph [0020]), and a pH manufacture agent (page 18, paragraph [0017]).

Therefore, contrary to Applicant's assertions, since the compounds of Kawai et al. meet all the structural limitations of the claimed compounds, absent evidence to the contrary, the compounds of Kawai et al. would inherently function as a compound that is suitable for non-parenteral administration.

***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 87-96 are rejected under 35 U.S.C. 102(b) as being anticipated by Nielsen et al. Nielsen et al. discloses pharmaceutical compositions that are intended for application to or through the mucosa of an animal, wherein the mucosa is preferably selected from oral, nasal, vaginal, rectal, aural, lung, and gastrointestinal mucosa (page 3, lines 4-8) . In one embodiment of the Nielsen et al. invention, the pharmaceutical composition comprises a biologically active substance, wherein said substance is ISIS-2922 (page 14, lines 19-22), which is an anti-herpes virus agent that is a phosphorothioate modified antisense oligonucleotide according to SEQ ID NO: 48 of the instant application (see also the Registry report of the sequence of ISIS-2922).

The compositions of Nielsen et al. that are specifically for oral administration may comprise pharmaceutically acceptable carriers or excipients, which may include (*inter alia*) penetration enhancers, ointment bases, excipients, emulsifying agents (i.e. forming an emulsion), and chelating agents (page 22, lines 5-12). The compositions or formulations of Nielsen et al. may also comprise emulsions, see page 21, lines 4-8, The ointment bases of Nielsen et al. include fatty acids such as vegetable oils, and palmitate (page 23, lines 9-11).

Nielsen et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

6. Claims 1, 4-7, 15, and 84 remain rejected under 35 U.S.C. 102(e) as being anticipated by Hnatowich et al. (see entire document), for the reasons of record.

Applicant's arguments filed 2-27-03 have been fully considered but are not persuasive. Applicants traverse the instant rejection on the grounds that the Hnatowich et al. reference does not teach or suggest antisense oligonucleotides that modulate expression of a cellular adhesion protein, modulation of a rate of cellular proliferation, or biological activity against eukaryotic pathogens or retroviruses. However, contrary to Applicant's assertions, the antisense oligonucleotides of Hnatowich et al. function by antagonizing the normal biological activity of tumor-specific or infectious DNA (col. 8, lines 29-40). Therefore, the antisense compounds of Hnatowich et al. function to modulate a rate of cellular proliferation associated with tumor-specific DNA, or has biological activity against eukaryotic pathogens which comprise infectious DNA.

***Claim Rejections - 35 USC § 103***

7. Claims 12-13, 80, and 85 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kawai et al. in view of New et al., Bennett et al. (5,843,738), and Nielsen et al. for the reasons of record.

Applicant's arguments filed 2-27-03 have been fully considered but are not persuasive. Applicants traverse the instant rejection on the grounds that the examiner has not legally provided sufficient motivation for combining antiviral ISIS-2922 in Nielson with the compositions of Kawai. Contrary to Applicant's assertions, since Applicant's have not provided any evidence of unexpected results associated with the claimed

compounds, as stated in the prior Office action, it would have been obvious to one of ordinary skill in the art at the time of filing to modify the compositions of Kawai et al. to further comprise bile salts, or to comprise the oligonucleotides disclosed in Bennett et al. and Nielsen et al. One of ordinary skill in the art would have been motivated to make this modification since the compositions of Kawai et al. are intended to provide carriers suitable for transducing gene DNA associated with cancer suppression genes, and DNA relevant to viral illness, and the antisense oligonucleotides of Bennett et al. and Nielsen et al. are disclosed as being useful for inhibiting the expression of genes associated with cancer (See Bennett et al., col. 6, lines 1-5) and viral infection (see abstract of Nielsen et al.), respectively. Moreover, one of ordinary skill in the art would have been motivated to modify the compositions of Kawai et al. with the bile salts of New et al. for the expressed benefits of the presence of bile salts in pharmaceutical compositions according to New et al., specifically wherein the bile salts function to improve absorption of biologically active materials into cells.

Applicant's arguments do not take the place of evidence that Applicant's claimed invention are unobvious over the teachings of Kawai et al. in view of Bennett et al. and New et al.

***Conclusion***

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

SEAN McGARRY
PRIMARY EXAMINER
1635

*JLE*
August 25, 2003